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Epoxy-functional sterically-stabilized diblock copolymer nanoparticles via RAFT aqueous emulsion polymerization: comparison of two synthetic strategies

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Abstract. Polymerization-induced self-assembly (PISA) is a powerful and versatile technique for the synthesis of a wide range of sterically-stabilized diblock copolymer nano-objects. Recently, we have used PISA to prepare epoxy-functional diblock copolymer worms and spheres directly in aqueous solution by incorporating glycidyl methacrylate into the *core-forming* hydrophobic block. Herein we examine the synthesis of diblock copolymer spheres via RAFT aqueous emulsion polymerization of benzyl methacrylate in which the epoxy groups are exclusively located within a non-ionic poly(glycerol monomethacrylate)-based *stabilizer* block. Two synthetic strategies have been explored: (i) using an epoxy-functional RAFT CTA to place an epoxy group at the terminus of every stabilizer block and (ii) incorporation of approximately one glycidyl methacrylate per stabilizer chain via copolymerization of glycidyl methacrylate with glycerol monomethacrylate (GMA). The epoxy groups conferred by the glycidyl methacrylate comonomer proved to be significantly more resistant to hydrolysis than those introduced using the epoxy-functional RAFT CTA. The former epoxy-functional nanoparticles were subsequently reacted with various water-soluble thiols to modify their electrophoretic behavior. Such nanoparticles are expected to offer potential applications in the context of mucoadhesion.

Introduction

Over the past twenty-five years, living radical polymerization techniques have revolutionized the synthetic polymer chemist's ability to design a wide range of well-defined functional block copolymers.[1-4] Such radical-based chemistries are highly attractive because they are exceptionally tolerant of monomer functionality and can be performed in many solvents, including protic solvents such as water.[5-10] In particular, reversible addition-fragmentation chain transfer (RAFT) polymerization is becoming increasingly widely used by many research groups.[11-26] This technique is based on the principle of rapid reversible chain transfer, which is conferred by the use of organosulfur compounds such as trithiocarbonates, dithiobenzoates or xanthates.[23-28] Such chain transfer agents (CTAs) enable useful functionality such as carboxylic acid,[8, 29-32] hydroxyl,[32] tertiary amines,[33, 34] quaternary amines,[8]

alkyne,[35, 36] sulfonates,[8] azide,[37-40] and epoxy groups[41, 42] to be readily introduced at the polymer chain-ends.[22, 43] RAFT polymerization has been conducted under various conditions, including bulk, solution, emulsion, dispersion, suspension and miniemulsion polymerization.[14, 23, 44-47] Of particular relevance to the present work, RAFT polymerization has been exploited for the synthesis of well-defined amphiphilic diblock copolymers.[14, 23, 48-50]

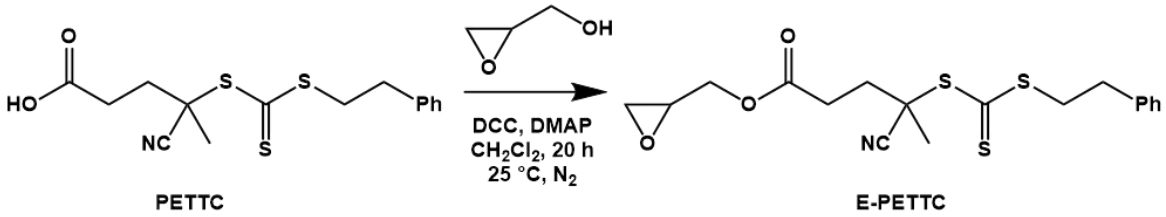
Over the past decade or so, polymerization-induced self-assembly (PISA) has become widely recognized as a powerful platform technology for the rational design of block copolymer nanoparticles of various morphologies, including spheres, worms, vesicles, framboidal vesicles and lamellae.[44, 51-64] In the specific context of RAFT aqueous emulsion polymerization, PISA typically involves chain extension of a water-soluble polymer precursor using a water-immiscible monomer such as styrene,[65-73] benzyl methacrylate,[74, 75] 2,2,2-trifluoroethyl methacrylate[76], methyl methacrylate[71, 77] or *n*-butyl acrylate.[77-81] At a certain critical degree of polymerization (DP) the growing hydrophobic block becomes insoluble in the aqueous phase, which drives *in situ* self-assembly to form sterically-stabilized diblock copolymer nano-objects.

It is well-known that the highly-strained, electrophilic nature of the oxirane ring facilitates its orthogonal transformation into many useful functional groups.[82] In the context of synthetic polymer chemistry, glycidyl methacrylate (GlyMA) is widely regarded as a highly versatile monomer: its pendent epoxy group can be readily reacted with thiols, amines, carboxylic acids, azides and water.[83-87] Recently, we reported the RAFT aqueous emulsion polymerization of glycidyl methacrylate to produce spherical diblock copolymer nanoparticles containing epoxy groups in the *core-forming* block.[88] In contrast, we examine herein the synthesis of spherical diblock copolymer nanoparticles in which the epoxy groups are exclusively located within the *stabilizer* chains. In this context, Ratcliffe et al.[85] reported the reaction of epoxy groups located within the stabilizer chains of block copolymer worms using epoxy-amine chemistry. In contrast, we explore the derivatization of epoxy groups using epoxy-thiol chemistry. Two synthetic strategies have been explored: (i) using an epoxy-functional RAFT CTA to place an epoxy group at the terminus of every stabilizer block and (ii) incorporation of approximately one glycidyl methacrylate per stabilizer chain via copolymerization of glycidyl methacrylate with glycerol monomethacrylate (GMA). In both cases, the precursor epoxy-functional nanoparticles are reacted with various thiols to modify their electrophoretic behaviour.

Results and Discussion

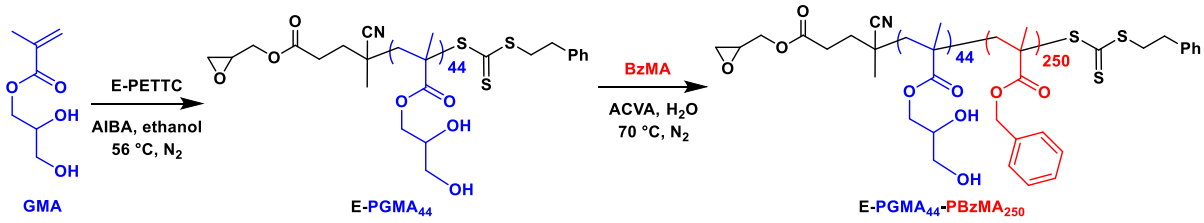
Recently we reported the PISA synthesis of several examples of epoxy-functional diblock copolymer nano-objects in aqueous solution.[85-88] In each case, GlyMA was utilized as a convenient comonomer to introduce the epoxy groups. When placed in the core-forming block, the epoxy groups can be used to crosslink the nanoparticle cores using either epoxy-amine or epoxy-thiol chemistry.[86-88] When placed in the steric stabilizer block, post-polymerization modification of the epoxy groups either enables crosslinks to be introduced between nanoparticles or provides a convenient route to modify their surface chemistry.[85]

In principle, using an epoxy-functional RAFT CTA provides significantly better control over the spatial location of the epoxy groups, since they are placed exclusively at the terminus of the stabilizer chains, rather than being distributed statistically within the steric stabilizer chains. This inspired us to synthesize the epoxy-functional RAFT CTA shown in Scheme 1 via Steglich esterification of a carboxylic acid-functionalized trithiocarbonate-based RAFT agent (PETTC).



Scheme 1. Synthesis of an epoxy-functional RAFT CTA (E-PETTC) via Steglich esterification.

The desired E-PETTC RAFT CTA was isolated in good yield (62%), characterized by ^{1}H NMR spectroscopy (see Figure S1) and subsequently used for the synthesis of (i) a well-defined epoxy-functional poly(glycerol monomethacrylate) [E-PGMA$_{44}$] macro-CTA and (ii) epoxy-functional poly(glycerol monomethacrylate)-poly(benzyl monomethacrylate) [E-PGMA$_{44}$-PBzMA$_{250}$] nanoparticles via RAFT aqueous emulsion polymerization of BzMA (see Scheme 2). ^{1}H NMR studies suggest that most of the epoxy groups survive the polymerization conditions employed for the synthesis of the macro-CTA (>95%) and the diblock copolymer (>90%) respectively, which is consistent with observations reported by Chambon et al.[89] for related aqueous PISA formulations.



Scheme 2. Synthesis of (i) an epoxy-functional poly(glycerol monomethacrylate) macro-CTA [E-PGMA$_{44}$] via RAFT aqueous solution polymerization of glycerol monomethacrylate using E-PETTC and (ii) epoxy-functional poly(glycerol monomethacrylate)-poly(benzyl methacrylate) [E-PGMA$_{44}$-PBzMA$_{250}$] nanoparticles via RAFT aqueous emulsion polymerization of benzyl methacrylate at 70 °C.

However, DMF GPC analysis of the final E-PGMA$_{44}$-PBzMA$_{250}$ nanoparticles indicated a relatively broad molecular weight distribution (M_w/M_n = 1.53), see Figure 1a. Significantly narrower molecular weight distributions (M_w/M_n < 1.30) were reported by Cunningham and co-workers for conventional PGMA$_{51}$-PBzMA$_x$ nanoparticles under the same conditions,[74] which suggests that some of the terminal epoxy groups reacted with the hydroxyl groups on the poly(glycerol monomethacrylate) stabilizer block during the RAFT aqueous emulsion polymerization of benzyl methacrylate. Indeed, we recently observed similar problems during the RAFT aqueous emulsion polymerization of glycidyl methacrylate at 70 °C.[88]

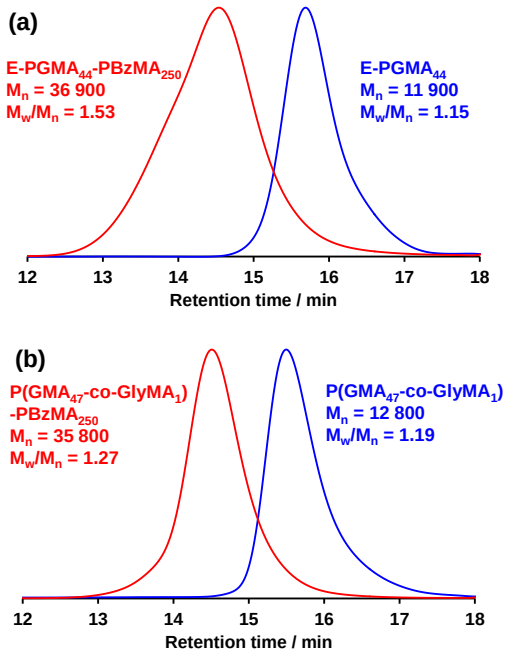
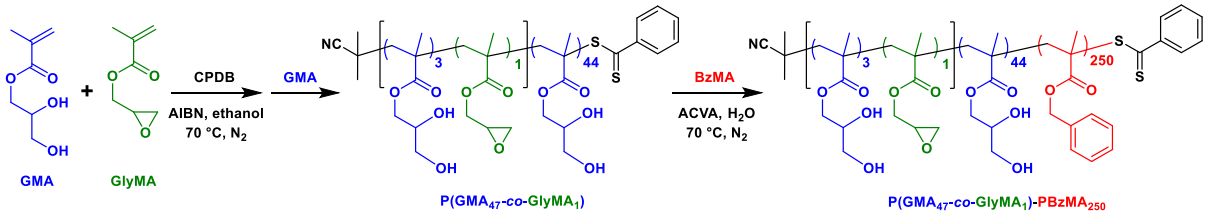


Figure 1. DMF GPC curves recorded for: (a) the E-PGMA$_{44}$ macro-CTA precursor and the corresponding E-PGMA$_{44}$-PBzMA$_{250}$ diblock copolymer prepared via RAFT aqueous emulsion polymerization of BzMA at 70 °C; (b) the P(GMA$_{47}$-*co*-GlyMA$_1$) macro-CTA precursor and the corresponding P(GMA$_{47}$-*co*-GlyMA$_1$)-PBzMA$_{250}$ diblock copolymer prepared via RAFT aqueous emulsion polymerization of BzMA at 70 °C.

Moreover, further investigations confirmed that the E-PGMA$_{44}$ macro-CTA is relatively unstable in aqueous solution at pH 8.5, which corresponds to the solution pH employed for the subsequent functionalization reactions described below. More specifically, ^{1}H NMR studies indicated that the terminal epoxy group on this precursor was rather prone to ring-opening hydrolysis by water to form the equivalent diol. Furthermore, some elimination also occurred under such conditions, generating glycidol as a small-molecule by-product (see Figure 2a). The relative intensities of the respective ^{1}H NMR signals suggests that the majority of the epoxy end-groups are hydrolyzed, rather than eliminated. These side-reactions limit the extent of derivatization that can be achieved using epoxy-thiol chemistry (see below).

In view of this unexpected problem, we decided to revisit the glycidyl methacrylate comonomer route but to prepare the epoxy-functional macro-CTA precursor via a two-step synthesis route similar to that recently reported by Yao and co-workers.[90] Thus, GlyMA was initially statistically copolymerized with GMA to afford an oligomer with a mean DP of 4. This precursor was then chain-extended with GMA to produce the desired P(GMA$_{47}$-*co*-GlyMA$_1$) macro-CTA (see Supporting Information for further details). This afforded a precursor with a relatively narrow molecular weight distribution (see Figure 1b) and a corresponding low-dispersity P(GMA$_{47}$-*co*-GlyMA$_1$)-PBzMA$_{250}$ diblock copolymer (M_w/M_n ~ 1.27). The latter result provides further indirect evidence for a branching side-reaction associated with the terminal epoxy groups during the RAFT aqueous emulsion polymerization of BzMA at 70 °C (compare Figures 1a and 1b).

Moreover, this alternative synthetic route also ensured that the epoxy groups were located near the periphery of the sterically-stabilized nanoparticles when this water-soluble macro-CTA was subsequently used for the RAFT aqueous emulsion polymerization of BzMA (see Scheme 3).



Scheme 3. (i) Synthesis of an epoxy-functional P(GMA_{47}-*co*-$GlyMA_1$) macro-CTA via RAFT aqueous solution copolymerization of glycerol monomethacrylate with glycidyl methacrylate. (ii) Synthesis of epoxy-functional P(GMA_{47}-*co*-$GlyMA_1$)-$PBzMA_{250}$ nanoparticles via RAFT aqueous emulsion polymerization of benzyl methacrylate using this P(GMA_{47}-*co*-$GlyMA_1$) macro-CTA at 70 °C.

Encouragingly, ^{1}H NMR studies indicated that the pendent epoxy group in this P(GMA_{47}-*co*-$GlyMA_1$) macro-CTA was much more stable towards hydrolysis than that in the E-$PGMA_{44}$ macro-CTA during long-term storage in aqueous solution at pH 8.5 (see Figure 2b). Presumably, this reflects the greater steric congestion for the methacrylic ester group in the GlyMA repeat unit compared to the relatively exposed ester end-groups produced when using the epoxy-functional RAFT CTA.

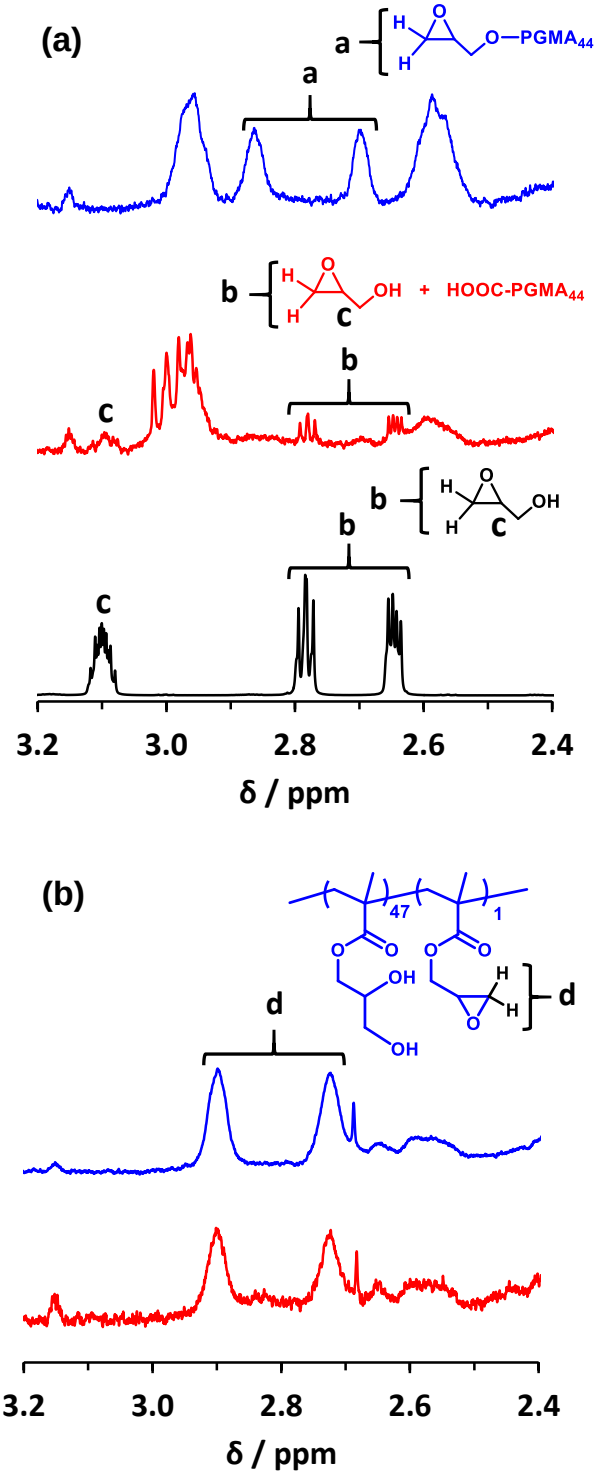


Figure 2. (a) Partial ^{1}H NMR spectra (CD_3OD) recorded for the E-$PGMA_{44}$ macro-CTA, before (upper spectrum) and after (middle spectrum) ageing as an aqueous solution for 16 h at pH 8.5. A ^{1}H NMR spectrum recorded for glycidol in CD_3OD is also included as a reference (lower spectrum). Clearly, the epoxy ring does not survive such storage conditions and peak integration suggests that both hydrolysis and elimination side-reactions occur. (b) Partial ^{1}H NMR spectra (CD_3OD) recorded for the P(GMA_{47}-*co*-$GlyMA_1$) macro-CTA before (upper spectrum) and after (lower spectrum) ageing as an aqueous solution for 16 h at pH 8.5. In this case, the epoxy groups are clearly much more resistant to hydrolysis and elimination side-reactions.

We recently reported that epoxy-thiol chemistry can be used to crosslink the cores of epoxy-functional diblock copolymer worms in aqueous solution at 20 °C.[91] Thus we explored whether this chemistry could be utilized for the surface modification of the epoxy-decorated nanoparticles described above. These reactions were conducted at pH 8.5, hence the thiol is in its more reactive thiolate form (pK_a ~ 8.2) and the amine group on cysteamine (pK_a ~ 10.7) remains protonated to prevent epoxy-amine side-reactions. Furthermore, a twenty-fold excess of thiol groups relative to epoxy groups was utilized to minimize the possibility of side reactions between the amine (or carboxylic acid) group and the epoxy ring. Moreover, Ratcliffe and co-workers demonstrated that reacting a twenty-fold excess of a diamine reagent relative to pendent epoxy groups was sufficient to ensure monofunctionalization (i.e. only one primary amine reacted to form a secondary amine).[85] Indeed, ^{1}H NMR studies of the P(GMA_{47}-*co*-$GlyMA_1$) macro-CTA confirm the success of such epoxy-thiol reactions when using either cysteamine or 3-mercaptopropanoic acid (see Figure S2).

Scanning electron microscopy (SEM) studies confirmed a well-defined spherical morphology for the E-$PGMA_{44}$-$PBzMA_{250}$ nanoparticles and epoxy-functional P(GMA_{47}-*co*-$GlyMA_1$)-$PBzMA_{250}$ nanoparticles (see Figure 3). Dynamic light scattering (DLS) analysis indicated relatively narrow size distributions in each case: the former nanoparticles had a pH-independent DLS diameter of around 83 nm (PDI = 0.06), while the latter nanoparticles had a pH-independent mean hydrodynamic diameter of around 75 nm n (PDI < 0.10).

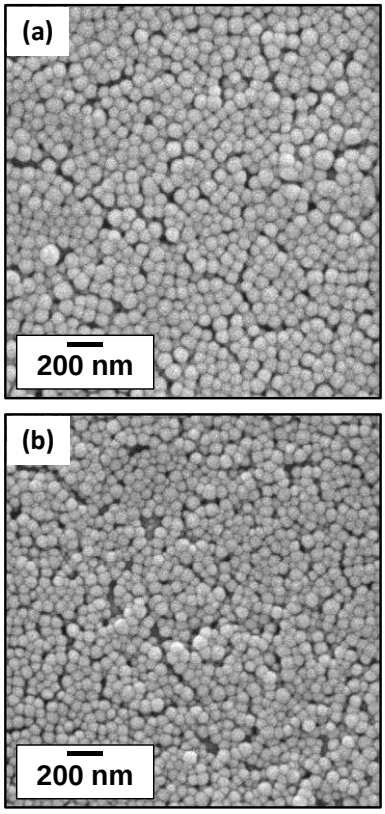
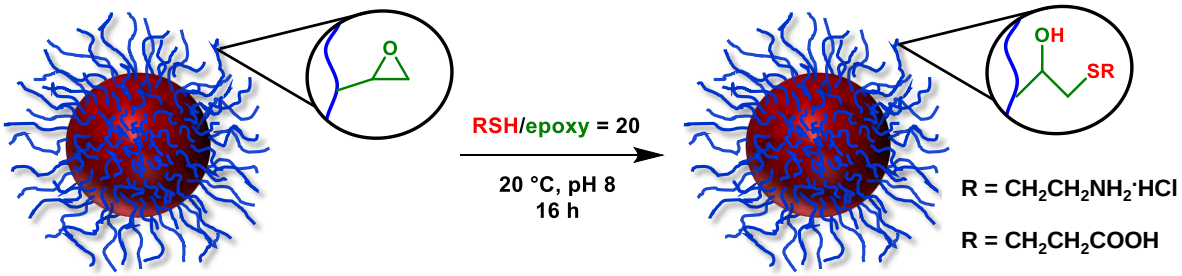


Figure 3. Representative SEM images obtained for (a) the E-$PGMA_{44}$-$PBzMA_{250}$ nanoparticles and (b) the epoxy-functional P(GMA_{47}-*co*-$GlyMA_1$)-$PBzMA_{250}$ nanoparticles, confirming their well-defined spherical morphology in each case.

As expected, aqueous electrophoresis studies indicated only very weak anionic character for these precursor spherical nanoparticles, with zeta potential of -2 to -5 mV being obtained over a wide pH

range (see Figure 4). For comparison, the corresponding E-PGMA$_{44}$-PBzMA$_{250}$ nanoparticles exhibited slightly higher negative zeta potentials (-10 mV) at alkaline pH (see Figure S3).

Moreover, ^{1}H NMR studies indicated that the P(GMA$_{47}$-*co*-GlyMA$_{1}$)-PBzMA$_{250}$ nanoparticles retained their epoxy functionality after the RAFT aqueous emulsion polymerization of BzMA (see Figure S4). Reaction of a twenty-fold excess of either 3-mercaptopropanoic acid or cysteamine with these epoxy groups (see Scheme 4) led to a significant change in the electrophoretic behavior of the nanoparticles (see Figure 4).



Scheme 4. Schematic derivatization of epoxy-functional P(GMA$_{47}$-*co*-GlyMA$_{1}$)-PBzMA$_{250}$ nanoparticles at 20 °C via their reaction with water-soluble functional thiols (either cysteamine or 3-mercaptopropanoic acid in its sodium salt form) at pH 8. Subsequent aqueous electrophoresis studies indicate that this epoxy-thiol chemistry was successful (see Figure 4).

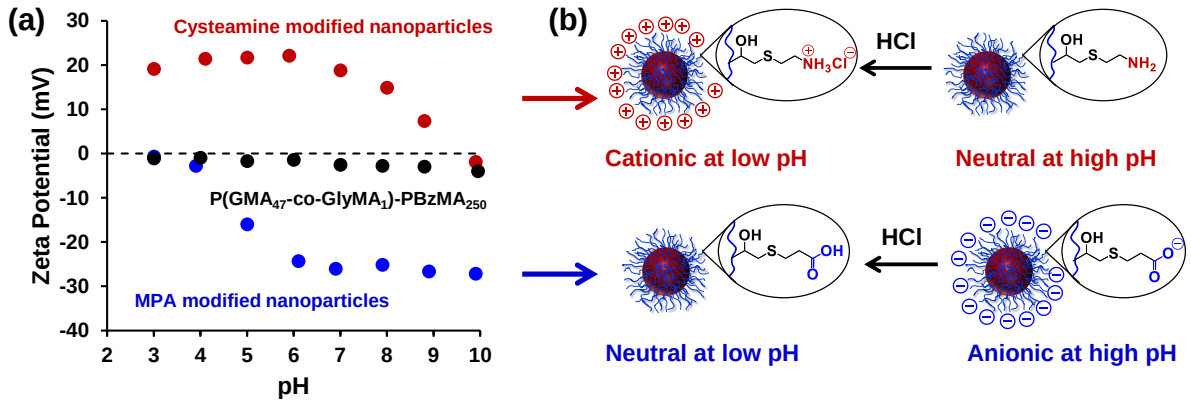


Figure 4. (a) Aqueous electrophoresis data obtained for the P(GMA$_{47}$-*co*-GlyMA$_{1}$)-PBzMA$_{250}$ spherical nanoparticles before and after reaction with either cysteamine or 3-mercaptopropanoic acid (MPA). (b) Schematic cartoon illustrating the surface charge of the derivatized nanoparticles at high and low pH. Clearly, epoxy-thiol derivatization has been successful in both cases: the primary amine groups confer cationic character at low pH, while the carboxylic acid groups confer anionic character at high pH.

Incorporating the former reagent within the steric stabilizer chains confers significant *anionic* character above pH 6, as well as the pH-sensitivity anticipated for isolated pendent carboxylic acid groups at lower pH. In contrast, the latter reagent produces nanoparticles with appreciable *cationic* character: zeta potentials are approximately +20 mV between pH 3 and pH 7 and there is an isoelectric point at around pH 9.5. Thus these epoxy-thiol reactions clearly produce nanoparticles decorated with either amine (cysteamine) or carboxylic acid (3-mercaptopropanoic acid) groups. For comparison, the

corresponding aqueous electrophoresis data obtained when reacting the epoxy groups of the E-PGMA$_{44}$-PBzMA$_{250}$ nanoparticles with either cysteamine or 3-mercaptopropanoic acid are shown in Figure S3. Using the former reagent, only weakly cationic character (zeta potential ~ +13 mV) is observed at low pH. With the latter reagent, appreciable anionic character is observed at high pH (zeta potential ~ −28 mV). However, in this case it is noteworthy that premature elimination of the terminal epoxy group via ester hydrolysis would also confer a carboxylic acid end-group, in addition to that formed via reaction of the 3-mercaptopropanoic acid. Finally, DMF GPC analysis of the P(GMA$_{47}$-*co*-GlyMA$_1$)-PBzMA$_{250}$ diblock copolymer chains confirmed that the narrow molecular weight distribution exhibited by the precursor was retained in the final cysteamine- or 3-mercaptopropanoic acid-derivatized copolymer (see Figure S5).

We plan to evaluate the mucoadhesion properties of these new functional sterically-stabilized nanoparticles in due course. For such applications, the chemical functionalities most often exploited are amines, thiols and hydroxyl groups.[92-94] The latter are conferred by the GMA residues on the stabilizer chains, while the former can be readily introduced via reaction with cysteamine, as demonstrated in the present study. In principle, thiol functionality can be introduced by reacting the pendent epoxy groups using an excess of a suitable water-soluble dithiol such as 2,2'-(ethylenedioxy)diethanethiol. It is perhaps also noteworthy that the epoxy functionality alone may well enable efficient chemical grafting of these nanoparticles to biological tissues, hence promoting strong, irreversible (muco)adhesion via epoxy-amine chemistry.

Conclusions

In principle, the epoxy-functional RAFT CTA described herein enables the precise placement of epoxy groups at the periphery of sterically-stabilized nanoparticles prepared via PISA. In practice, the synthetic utility of this CTA appears to be rather limited in aqueous media because its ester linkage is susceptible to hydrolysis. As an alternative, similar epoxy-functional nanoparticles can be readily prepared via PISA by using glycidyl methacrylate as a comonomer when synthesizing the water-soluble steric stabilizer block. Although the spatial location of such epoxy groups is less precise, they are much more stable with respect to *in situ* hydrolysis. These epoxy groups can be reacted with water-soluble thiols to introduce either amine or carboxylic acid functionality, which is shown to dictate the electrophoretic mobility of the nanoparticles. Such model nanoparticles are expected to offer potential applications in the context of mucoadhesion.

Acknowledgements

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References

1. J. Chiefari, Y. K. Chong, F. Ercole, J. Krstina, J. Jeffery, T. P. T. Le, R. T. A. Mayadunne, G. F. Meijs, C. L. Moad, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 1998, **31**, 5559-5562.
2. M. Kato, M. Kamigaito, M. Sawamoto and T. Higashimura, *Macromolecules*, 1995, **28**, 1721-1723.

3. J.-S. Wang and K. Matyjaszewski, *Journal of the American Chemical Society*, 1995, **117**, 5614-5615.
4. C. J. Hawker, A. W. Bosman and E. Harth, *Chemical Reviews*, 2001, **101**, 3661-3688.
5. X. S. Wang and S. P. Armes, *Macromolecules*, 2000, **33**, 6640-6647.
6. A. B. Lowe and C. L. McCormick, *Australian Journal of Chemistry*, 2002, **55**, 367-379.
7. C. L. McCormick and A. B. Lowe, *Accounts of Chemical Research*, 2004, **37**, 312-325.
8. J.-F. Baussard, J.-L. Habib-Jiwan, A. Laschewsky, M. Mertoglu and J. Storsberg, *Polymer*, 2004, **45**, 3615-3626.
9. M. Mertoglu, A. Laschewsky, K. Skrabania and C. Wieland, *Macromolecules*, 2005, **38**, 3601-3614.
10. M. K. Georges, J. L. Lukkarila and A. R. Szkurhan, *Macromolecules*, 2004, **37**, 1297-1303.
11. D. J. Keddie, *Chemical Society Reviews*, 2014, **43**, 496-505.
12. G. Moad, E. Rizzardo and S. H. Thang, *Australian Journal of Chemistry*, 2005, **58**, 379-410.
13. G. Moad, E. Rizzardo and S. H. Thang, *Australian Journal of Chemistry*, 2009, **62**, 1402-1472.
14. G. Moad, E. Rizzardo and S. H. Thang, *Australian Journal of Chemistry*, 2012, **65**, 985-1076.
15. M. S. Donovan, T. A. Sanford, A. B. Lowe, B. S. Sumerlin, Y. Mitsukami and C. L. McCormick, *Macromolecules*, 2002, **35**, 4570-4572.
16. C. L. McCormick, B. S. Sumerlin, B. S. Lokitz and J. E. Stempka, *Soft Matter*, 2008, **4**, 1760-1773.
17. M. R. Hill, R. N. Carmean and B. S. Sumerlin, *Macromolecules*, 2015, **48**, 5459-5469.
18. H. Willcock and R. K. O'Reilly, *Polymer Chemistry*, 2010, **1**, 149-157.
19. C. Barner-Kowollik, M. Buback, B. Charleux, M. L. Coote, M. Drache, T. Fukuda, A. Goto, B. Klumperman, A. B. Lowe, J. B. Mcleary, G. Moad, M. J. Monteiro, R. D. Sanderson, M. P. Tonge and P. Vana, *Journal of Polymer Science Part A: Polymer Chemistry*, 2006, **44**, 5809-5831.
20. A. B. Lowe and C. L. McCormick, *Progress in Polymer Science*, 2007, **32**, 283-351.
21. L. Barner, T. P. Davis, M. H. Stenzel and C. Barner-Kowollik, *Macromolecular Rapid Communications*, 2007, **28**, 539-559.
22. G. Moad, *Polymer Chemistry*, 2017, **8**, 177-219.
23. S. Perrier and P. Takolpuckdee, *Journal of Polymer Science Part A: Polymer Chemistry*, 2005, **43**, 5347-5393.
24. G. Moad, E. Rizzardo and S. H. Thang, *Polymer*, 2008, **49**, 1079-1131.
25. M. Destarac, C. Brochon, J. M. Catala, A. Wilczewska and S. Z. Zard, *Macromolecular Chemistry and Physics*, 2002, **203**, 2281-2289.
26. M. Destarac, W. Bzducha, D. Taton, I. Gauthier-Gillaizeau and S. Z. Zard, *Macromolecular Rapid Communications*, 2002, **23**, 1049-1054.
27. R. T. A. Mayadunne, E. Rizzardo, J. Chiefari, J. Krstina, G. Moad, A. Postma and S. H. Thang, *Macromolecules*, 2000, **33**, 243-245.
28. D. Charmot, P. Corpart, H. Adam, S. Z. Zard, T. Biadatti and G. Bouhadir, *Macromolecular Symposia*, 2000, **150**, 23-32.
29. J. R. Lovett, N. J. Warren, S. P. Armes, M. J. Smallridge and R. B. Cracknell, *Macromolecules*, 2016, **49**, 1016-1025.
30. J. R. Lovett, N. J. Warren, L. P. Ratcliffe, M. K. Kocik and S. P. Armes, *Angewandte Chemie*, 2015, **54**, 1279-1283.
31. M. Li, P. De, S. R. Gondi and B. S. Sumerlin, *Journal of Polymer Science Part A: Polymer Chemistry*, 2008, **46**, 5093-5100.
32. J. Skey and R. K. O'Reilly, *Chemical Communications*, 2008, 4183-4185.
33. N. J. W. Penfold, J. R. Lovett, P. Verstraete, J. Smets and S. P. Armes, *Polymer Chemistry*, 2017, **8**, 272-282.
34. N. J. W. Penfold, J. R. Lovett, N. J. Warren, P. Verstraete, J. Smets and S. P. Armes, *Polymer Chemistry*, 2016, **7**, 79-88.

35. R. Ranjan and W. J. Brittain, *Macromolecular Rapid Communications*, 2007, **28**, 2084-2089.
36. K. T. Wiss and P. Theato, *Journal of Polymer Science Part A: Polymer Chemistry*, 2010, **48**, 4758-4767.
37. S. R. Gondi, A. P. Vogt and B. S. Sumerlin, *Macromolecules*, 2007, **40**, 474-481.
38. I. F. Domínguez, J. Kolomanska, P. Johnston, A. Rivaton and P. D. Topham, *Polymer International*, 2015, **64**, 621-630.
39. Y.-S. Ye, Y.-N. Chen, J.-S. Wang, J. Rick, Y.-J. Huang, F.-C. Chang and B.-J. Hwang, *Chemistry of Materials*, 2012, **24**, 2987-2997.
40. G. Gody, C. Rossner, J. Moraes, P. Vana, T. Maschmeyer and S. Perrier, *Journal of the American Chemical Society*, 2012, **134**, 12596-12603.
41. A. Vora, M. J. Nasrullah and D. C. Webster, *Macromolecules*, 2007, **40**, 8586-8592.
42. S. Kaga, N. P. Truong, L. Esser, D. Senyschyn, A. Sanyal, R. Sanyal, J. F. Quinn, T. P. Davis, L. M. Kaminskas and M. R. Whittaker, *Biomacromolecules*, 2017, **18**, 3963-3970.
43. D. J. Keddie, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 2012, **45**, 5321-5342.
44. P. B. Zetterlund, S. C. Thickett, S. Perrier, E. Bourgeat-Lami and M. Lansalot, *Chemical Reviews*, 2015, **115**, 9745-9800.
45. J. D. Biasutti, T. P. Davis, F. P. Lucien and J. P. A. Heuts, *Journal of Polymer Science Part A: Polymer Chemistry*, 2005, **43**, 2001-2012.
46. M. F. Cunningham, *Progress in Polymer Science*, 2008, **33**, 365-398.
47. A. Butte, G. Storti and M. Morbidelli, *Macromolecules*, 2001, **34**, 5885-5896.
48. A. W. York, S. E. Kirkland and C. L. McCormick, *Advanced Drug Delivery Reviews*, 2008, **60**, 1018-1036.
49. Y. Li and S. P. Armes, *Angewandte Chemie*, 2010, **49**, 4042-4046.
50. A. E. Smith, X. Xu and C. L. McCormick, *Progress in Polymer Science*, 2010, **35**, 45-93.
51. B. Charleux, G. Delaittre, J. Rieger and F. D'Agosto, *Macromolecules*, 2012, **45**, 6753-6765.
52. N. J. Warren and S. P. Armes, *Journal of the American Chemical Society*, 2014, **136**, 10174-10185.
53. M. J. Derry, L. A. Fielding and S. P. Armes, *Progress in Polymer Science*, 2016, **52**, 1-18.
54. S. L. Canning, G. N. Smith and S. P. Armes, *Macromolecules*, 2016, **49**, 1985-2001.
55. J. Rieger, *Macromolecular Rapid Communications*, 2015, **36**, 1458-1471.
56. J. Yeow and C. Boyer, *Advanced Science*, 2017, **4**, 1700137.
57. S. Dong, W. Zhao, F. P. Lucien, S. Perrier and P. B. Zetterlund, *Polymer Chemistry*, 2015, **6**, 2249-2254.
58. Y. Pei, L. Thurairajah, O. R. Sugita and A. B. Lowe, *Macromolecules*, 2015, **48**, 236-244.
59. Y. W. Pei and A. B. Lowe, *Polymer Chemistry*, 2014, **5**, 2342-2351.
60. W. Zhou, Q. Qu, Y. Xu and Z. An, *ACS Macro Letters*, 2015, **4**, 495-499.
61. S.-l. Chen, P.-f. Shi and W.-q. Zhang, *Chinese Journal of Polymer Science*, 2017, **35**, 455-479.
62. J. Yeow, R. Chapman, J. Xu and C. Boyer, *Polymer Chemistry*, 2017, **8**, 5012-5022.
63. B. Karagoz, L. Esser, H. T. Duong, J. S. Basuki, C. Boyer and T. P. Davis, *Polymer Chemistry*, 2014, **5**, 350-355.
64. A. B. Lowe, *Polymer*, 2016, **106**, 161-181.
65. D. E. Ganeva, E. Sprong, H. de Bruyn, G. G. Warr, C. H. Such and B. S. Hawkett, *Macromolecules*, 2007, **40**, 6181-6189.
66. W. Zhang, F. D'Agosto, O. Boyron, J. Rieger and B. Charleux, *Macromolecules*, 2012, **45**, 4075-4084.
67. N. P. Truong, M. V. Dussert, M. R. Whittaker, J. F. Quinn and T. P. Davis, *Polymer Chemistry*, 2015, **6**, 3865-3874.
68. C. St Thomas, R. Guerrero-Santos and F. D'Agosto, *Polymer Chemistry*, 2015, **6**, 5405-5413.
69. M. Manguian, M. Save and B. Charleux, *Macromolecular Rapid Communications*, 2006, **27**, 399-404.

70. X. Zhang, S. Boissé, W. Zhang, P. Beaunier, F. D'Agosto, J. Rieger and B. Charleux, *Macromolecules*, 2011, **44**, 4149-4158.
71. I. Chaduc, M. Girod, R. Antoine, B. Charleux, F. D'Agosto and M. Lansalot, *Macromolecules*, 2012, **45**, 5881-5893.
72. W. Zhang, F. D'Agosto, O. Boyron, J. Rieger and B. Charleux, *Macromolecules*, 2011, **44**, 7584-7593.
73. Z. Jia, V. A. Bobrin, N. P. Truong, M. Gillard and M. J. Monteiro, *Journal of the American Chemical Society*, 2014, **136**, 5824-5827.
74. V. J. Cunningham, A. M. Alswieleh, K. L. Thompson, M. Williams, G. J. Leggett, S. P. Armes and O. M. Musa, *Macromolecules*, 2014, **47**, 5613-5623.
75. X. Zhang, J. Rieger and B. Charleux, *Polymer Chemistry*, 2012, **3**, 1502-1509.
76. B. Akpinar, L. A. Fielding, V. J. Cunningham, Y. Ning, O. O. Mykhaylyk, P. W. Fowler and S. P. Armes, *Macromolecules*, 2016, **49**, 5160-5171.
77. J. Rieger, G. Osterwinter, C. Bui, F. Stoffelbach and B. Charleux, *Macromolecules*, 2009, **42**, 5518-5525.
78. C. J. Ferguson, R. J. Hughes, B. T. T. Pham, B. S. Hawkett, R. G. Gilbert, A. K. Serelis and C. H. Such, *Macromolecules*, 2002, **35**, 9243-9245.
79. C. J. Ferguson, R. J. Hughes, D. Nguyen, B. T. T. Pham, R. G. Gilbert, A. K. Serelis, C. H. Such and B. S. Hawkett, *Macromolecules*, 2005, **38**, 2191-2204.
80. J. Rieger, F. Stoffelbach, C. Bui, D. Alaimo, C. Jerome and B. Charleux, *Macromolecules*, 2008, **41**, 4065-4068.
81. M. Chenal, L. Bouteiller and J. Rieger, *Polymer Chemistry*, 2013, **4**, 752-762.
82. M. B. Smith and J. March, *Advanced Organic Chemistry*, John Wiley & Sons, Inc., 2006.
83. M. Benaglia, A. Alberti, L. Giorgini, F. Magnoni and S. Tozzi, *Polymer Chemistry*, 2013, **4**, 124-132.
84. L. P. D. Ratcliffe, A. J. Ryan and S. P. Armes, *Macromolecules*, 2013, **46**, 769-777.
85. L. P. D. Ratcliffe, K. J. Bentley, R. Wehr, N. J. Warren, B. R. Saunders and S. P. Armes, *Polymer Chemistry*, 2017, **8**, 5962-5971.
86. J. R. Lovett, L. P. D. Ratcliffe, N. J. Warren, S. P. Armes, M. J. Smallridge, R. B. Cracknell and B. R. Saunders, *Macromolecules*, 2016, **49**, 2928-2941.
87. N. J. W. Penfold, Y. Ning, P. Verstraete, J. Smets and S. P. Armes, *Chemical Science*, 2016, **7**, 6894-6904.
88. F. L. Hatton, J. R. Lovett and S. P. Armes, *Polymer Chemistry*, 2017, **8**, 4856-4868.
89. P. Chambon, A. Blanazs, G. Battaglia and S. P. Armes, *Langmuir*, 2012, **28**, 1196-1205.
90. H. Yao, Y. Ning, C. P. Jesson, J. He, R. Deng, W. Tian and S. P. Armes, *ACS Macro Letters*, 2017, **6**, 1379-1385.
91. N. J. W. Penfold, A. J. Parnell, M. Molina, P. Verstraete, J. Smets and S. P. Armes, *Langmuir*, 2017, **33**, 14425-14436.
92. A. Bernkop-Schnürch and S. Steininger, *International Journal of Pharmaceutics*, 2000, **194**, 239-247.
93. A. Storha, E. A. Mun and V. V. Khutoryanskiy, *RSC Advances*, 2013, **3**, 12275-12279.
94. G. S. Irmukhametova, G. A. Mun and V. V. Khutoryanskiy, *Langmuir*, 2011, **27**, 9551-9556.